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Ischemic Burden in Silent and Painful Myocardial Ischemia: A Quantitative Exercise Sestamibi Tomographic Study

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Objectives. **We sought to determine whether the amount of myocardial ischemic burden differs in patients with painful or silent myocardial hypoperfusion during exercise testing.**

Background. **Whether a lack of symptoms during ischemia reflects an alteration in pain perception or less myocardium in jeopardy remains a controversial issue.**

Methods. **We studied 300 consecutive patients with a well established history of ischemic heart disease and reversible hypoperfusion on exercise sestamibi tomography. Rest and stress sestamibi defects were quantitatively assessed and indexes of exercise left ventricular dilation derived.**

Results. **Painful and silent reversible ischemia was observed in 97 (32%) and 203 (68%) patients, respectively. Patients with painful ischemia had lower values for work load, exercise time and peak rate-pressure product ($p < 0.01$) and more frequently showed significant ST segment depression during exercise than did patients with silent ischemia (69% vs. 40%, $p < 0.001$). On sestamibi tomography, patients with painful ischemia had more reversible hypoperfusion than did patients with silent ischemia (mean ± SD 16 ± 10% vs. 11 ± 7%, $p < 0.001$), despite a comparable extent of stress hypoperfusion (22 ± 12% vs. 22 ± 13%); they also had a higher endocardial dilation index (1.32 ± 0.32 vs. 1.10 ± 0.26, $p < 0.001$). By multivariate logistic analysis, the most powerful correlate of painful ischemia was a history of effort angina; the extent of reversible perfusion defect was the sole independent scintigraphic correlate of painful ischemia.**

Conclusions. **To our knowledge, this is the largest study comparing the degree of hypoperfusion and the presence of symptoms during exercise stress testing in a consecutive cohort of patients with ischemic heart disease and reversible hypoperfusion. The results suggest that the ischemic burden is greater in painful than in silent ischemia.**

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The occurrence of painless myocardial ischemia during daily activity and during exercise testing is common in patients with coronary artery disease (1–5). Whether the absence of pain depends on a hampered pain responsiveness or indicates that the degree of ischemic injury is not severe enough for the occurrence of pain is still largely debated (6–10), and previous studies assessing myocardial perfusion during exercise testing (9,11–19) have reported conflicting results. However, these studies used miscellaneous criteria in selecting patients, different imaging techniques and qualitative or semiquantitative criteria in interpreting the scintigraphic results.

Accordingly, in a large population of well defined subjects with ischemic heart disease undergoing exercise technetium-99m (^{99m}Tc) sestamibi myocardial tomography, we used quantitative analysis of the scintigraphic perfusion abnormalities to assess whether the ischemic burden is more severe in patients with chest pain during exercise than in those with silent ischemic episodes.

Methods

Study cohort. The study group consisted of 300 consecutive patients referred between January 1993 and December 1995 to our nuclear cardiology laboratory for stress-rest ^{99m}Tc sestamibi perfusion scintigraphy. This sample of patients was prospectively recruited according to the following selection criteria: 1) documented coronary artery disease based on angiography or a history of prior myocardial infarction (200 patients, 67%) or a high (>80%) pretest probability of coronary disease according to a Bayesian analysis of risk factors, symptoms and results of an exercise electrocardiogram (ECG) (100 patients, 33%) (9); and 2) unequivocal evidence of a reversible perfusion defect by quantitative criteria on exercise sestamibi tomography. The diagnosis of previous myocardial infarction was supported by a history of prolonged chest pain associated with a typical pattern of serum myocardial enzyme and evolutionary ECG changes. Patients with an uninterpretable ECG were excluded, as were those with rest ST segment abnormalities, conduction disturbances or left ventricular hypertrophy. Patients with recent myocardial infarction (<30 days) and those receiving digoxin were also excluded, as well as

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Abbreviations and Acronyms

ECG = electrocardiogram, electrocardiographic
TDI = transient dilation index

subjects who did not achieve a symptom-limited end point during exercise testing.

Exercise testing. Rest and exercise scans were performed in random in a 2-day imaging protocol. All rest studies were performed while the patient was receiving full therapy. All patients underwent a multistage symptom-limited exercise test in the upright position after an overnight fast and with medications withheld ≥12 h before stress testing; a 12-lead ECG was recorded every 1 min and blood pressure every 3 min. The work load was increased by 25 W every 3 min and patients exercised until they achieved the maximal predicted heart rate, reported exercise-limiting fatigue, chest pain, dyspnea or hypotension or had complex ventricular arrhythmias or ≥0.3 mV downsloping or horizontal ST segment depression. Throughout the exercise study and in the recovery period, patients were questioned by the cardiologist who supervised the test (C.M., M.G.) concerning the development of typical chest discomfort or any other clear anginal equivalent (i.e., pain in the neck, jaw, throat or arms). At peak exercise the tracer was injected, after which patients were encouraged to continue exercising for 60 to 90 s. An ECG response was defined as positive for ischemia if there was horizontal or downsloping ST segment depression ≥0.1 mV for ≥80 ms after the J point and for ≥3 consecutive beats.

Sestamibi images acquisition and processing. After the tracer injection (925 MBq/70 kg for both rest and stress studies), a light meal was provided to accelerate hepatobiliary clearance of the tracer and to improve the heart/background ratio. Scintigraphic image acquisition was performed within 60 min of tracer injection with use of a rotating camera (SP-6, Elscint, Israel) equipped with a high resolution parallel hole collimator and a ±10% energy window centered on the 140-keV photopeak. The camera head was rotated in a 180° arc in a circular orbit from the 30° right anterior oblique angle to the 30° left posterior angle with 3° increments every 20 s, in step-and-shoot mode. Data were collected in a 64 × 64 array. Care was taken to avoid major artifacts, such as patient motion during acquisition. Transaxial slices were reconstructed by using a filtered back-projection algorithm with a modified Wiener filter, without attenuation or scatter correction; flood correction was applied during reconstruction. Short-axis and long-axis (horizontal and vertical) tomograms were reconstructed from the transaxial slices. All studies were processed by an experienced operator who was unaware of the patients' clinical and functional data. Quantitative analysis of myocardial sestamibi distribution was performed as previously described (20). From the transaxial sections, slices in the short-axis view were reconstructed, and the polar map of the regional sestamibi distribution was normalized for peak myocardial activity and compared with the normal limits obtained in 50 gender-matched subjects with <5% probability of coronary artery disease. Pixels with tracer uptake falling >2.5 SD below mean normal values were considered abnormal. Abnormal areas were corrected for spatial distortion (20) and then summed to obtain total left ventricular defect size at rest and after exercise, expressed as a percent of the left ventricular surface. A perfusion defect observed on the exercise study was considered reversible when changes in defect size from the stress to the rest scan exceeded the 95% confidence limits of the method variability (i.e., 4.8% of the left ventricular surface), as previously determined (20). A change in the extent of the perfusion defect from rest to exercise ≥15% of the total left ventricular surface was arbitrarily defined as severe exertional ischemia.

The epicardial and endocardial contours of the midventricular short-axis slice on rest and exercise images were automatically drawn; the corresponding areas were computed and the exercise/rest area ratios were calculated and defined as epicardial and endocardial transient dilation indexes (TDI), respectively.

Statistical analysis. Data are reported as mean value ±SD for continuous variables and as a proportion for categoric variables. Univariate analysis of categoric variables was performed by using chi-square analysis or the Fisher exact test. Comparisons of continuous data between groups were made by using the Student *t* test for unpaired data or one-way analysis of variance (ANOVA) for factorial analysis with the Scheffé F test. A stepwise logistic regression analysis (BMPD Statistical Software) was used to assess the independent value of the significant clinical, ergometric and scintigraphic univariate correlates of painful perfusion defects. A p value <0.05 (two-tailed) was considered significant.

Results

Patient characteristics. The study group consisted of 300 patients (259 men [86%]) with a mean age of 57 ± 9 years (range 33 to 79). A history of stable angina pectoris was present in 124 patients (41%); 152 patients (51%) had had a prior myocardial infarction. Coronary angiography, available in 141 patients (47%), showed significant stenosis (≥50% lumen diameter reduction) of one major coronary vessel in 46 patients (33%); 92 other patients (65%) had multiple vessel disease. By inclusion criteria, all patients had reversible perfusion defects. On the basis of the clinical response to exercise, patients were classified into those with chest pain during exercise (97 patients [32%]) and those without chest pain (203 patients [68%]). Table 1 lists pertinent demographic, clinical and angiographic results from the two groups. Age and coronary anatomy were similar in both groups; patients with painful ischemia more frequently had a history of effort angina and those with silent ischemia a history of previous myocardial infarction.

Exercise test results. Table 2 compares exercise data in patients with painful or silent ischemia. Patients with painful

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Table 1. Clinical Findings in Patients With Painful or Silent Reversible Sestamibi Perfusion Defects During Exercise

	Painful Ischemia (n = 97 [32%])	Silent Ischemia (n = 203 [68%])	p Value
Age (yr)	58 ± 8	56 ± 10	NS
Male/female	77/20	182/21	NS
History			
Hypertension	23 (24%)	56 (27%)	NS
Diabetes	5 (5%)	11 (5%)	NS
Hypercholesterolemia	24 (25%)	52 (26%)	NS
Body mass index (kg/m^2)	27 ± 3	25 ± 3	< 0.001
Previous MI	36 (37%)	116 (57%)	< 0.05
Effort angina	71 (73%)	53 (26%)	< 0.001
Rest and effort angina	13 (13%)	16 (8%)	NS
Medications			
Nitrates	49 (51%)	69 (34%)	< 0.01
Beta-blockers	46 (47%)	73 (36%)	< 0.01
Calcium antagonists	41 (42%)	59 (29%)	< 0.01
Angiography	46	95	
Single-vessel disease	14 (32%)	32 (34%)	
Multivessel disease	30 (68%)	62 (66%)	NS
Occluded vessels	25 (54%)	36 (38%)	0.09
Proximal LAD occlusion	5 (11%)	10 (11%)	NS
Left ventricular ejection fraction*	55 ± 11	52 ± 12	NS

*On biplane two-dimensional echocardiography or contrast ventriculography. Data are reported as mean values ±SD or number (%) of patients. LAD = left anterior descending coronary artery; MI = myocardial infarction.

ischemia exercised for a shorter time, achieving significantly lower values for work load, peak exercise heart rate and peak rate-pressure product. They also showed significant ST segment depression during exercise more frequently than did patients with silent ischemia and had a significantly shorter time to onset of ST segment depression.

Scintigraphic findings. Table 2 also reports the scintigraphic results for the two groups. The total extent of myocardial hypoperfusion on exercise sestamibi tomography was comparable in the two groups; however, the amount of reversible ischemia (i.e., the difference between stress and rest tracer uptake defect extent) was significantly greater in patients with painful ischemia. Figure 1 shows plots of the distribution of reversible sestamibi defect extent according to the presence or absence of chest pain during exercise. Severe exertional ischemia was also more common in patients with painful ischemia (Table 2); these patients also had a significantly greater endocardial TDI although epicardial TDI was similar in the two groups.

During exercise, 75 patients (25%) had both chest pain and significant ECG changes; 122 other patients (41%) showed reversible sestamibi defects in the absence of both symptoms and ECG changes. The remaining 103 patients showed silent ECG changes (81 patients, 27%) or typical chest pain in the absence of ECG signs of ischemia (22 patients, 7%). The total extent of exercise sestamibi defect was comparable among all four categories; however, patients with both chest pain and ECG changes during exercise showed the largest reversible defect and the greatest endocardial TDI ($p < 0.01$) (Fig. 2).

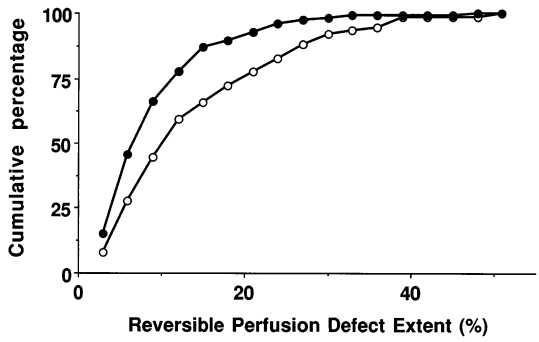
Table 2. Comparison of Exercise and Scintigraphic Data in Patients With Painful or Silent Reversible Sestamibi Perfusion Defects

	Painful Ischemia (n = 97 [32%])	Silent Ischemia (n = 203 [68%])	p Value
Exercise stress test			
Peak SBP (mm Hg)	189 ± 28	193 ± 25	< 0.001
Δ SBP (mm Hg)	45 ± 23	56 ± 27	< 0.01
Peak RPP (beats/min × mm Hg)	23,798 ± 6,275	27,458 ± 5,494	< 0.001
% of max age-predicted HR achieved	73 ± 22	81 ± 24	< 0.05
METs	4.7 ± 1.7	5.8 ± 1.8	< 0.001
Positive ECG finding	67 (69%)	81 (40%)	< 0.001
Time to 1-mm ST↓ (min)	7.1 ± 4.5	8.9 ± 3.2	< 0.05
Total time to ST↓ (*) (min)	11.1 ± 5.2	11.3 ± 5.5	NS
Amount of ST↓ (mm)	2.1 ± 0.9	2.0 ± 0.7	NS
Sestamibi SPECT			
Rest defect extent	5 ± 7%	10 ± 11%	< 0.01
Stress defect extent	22 ± 12%	22 ± 13%	NS
Reversible defect extent	16 ± 10%	11 ± 7%	< 0.001
Severe ischemia	29 (30%)	28 (14%)	< 0.001
Endocardial TDI	1.32 ± 0.32	1.10 ± 0.26	< 0.001
Epicardial TDI	1.0 ± 0.12	0.99 ± 0.19	NS
Perfusion defect location			
LAD territory	41 (42%)	94 (46%)	NS
RCA/LCx territory	67 (69%)	153 (75%)	NS

*Defined as time of ST segment depression during exercise plus time to full recovery. Data are reported as mean value ±SD or number (%) of patients. Δ SBP = change in systolic blood pressure from rest to exercise; ECG = electrocardiogram; HR = heart rate; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; max = maximal; METs = metabolic equivalents; RCA = right coronary artery; RPP = rate-pressure product; SBP = systolic blood pressure; SPECT = single-photon emission computed tomography; ST↓ = ST segment depression; TDI = transient dilation index.

Figure 3 shows the extent of reversible perfusion defect and endocardial TDI in different clinical subgroups of patients (previous myocardial infarction, presence of ECG signs of ischemia, single vs. multiple vessel disease) with respect to the presence of exertional angina. In all subgroups, patients with

Figure 1. Cumulative frequency distribution of extent of the reversible technetium-99m sestamibi uptake defect in the 97 patients with **(open circles)** and in the 203 patients without **(closed circles)** chest pain during exercise.



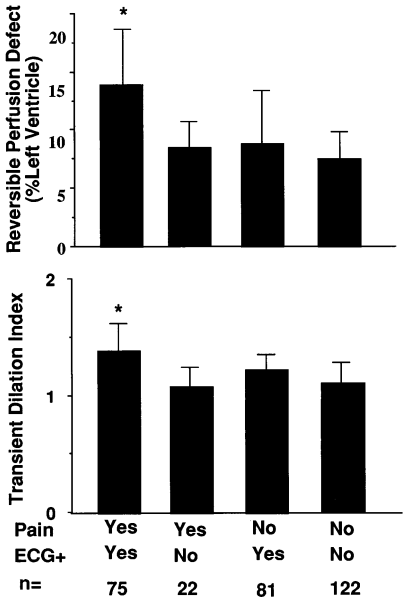


Figure 2. Bar graphs showing the extent of reversible hypoperfusion **(upper panel)** and the endocardial transient dilation index **(lower panel)** in patient cohorts grouped according to the presence of electrocardiographic changes (ECG+) and chest pain during exercise. Data are reported as mean value ±SE. *$p < 0.01$ versus other groups.

painful ischemia had a significantly greater reversible perfusion defect and endocardial TDI.

When the clinical, ergometric and scintigraphic variables that correlated significantly with painful ischemia on univariate analysis were introduced in a logistic regression analysis, a history of effort angina was found to be the most powerful predictor of painful ischemia (Table 3). The extent of reversible perfusion defect was the sole scintigraphic variable independently correlated with painful ischemia.

Figure 3. Bar graphs showing the extent of reversible hypoperfusion **(upper panel)** and the endocardial transient dilation index **(lower panel)** in different subgroups of patients with **(open bars)** and without **(closed bars)** chest pain during exercise. Data are reported as mean value ±SE. *$p < 0.01$. MI = myocardial infarction; MVD = multivessel disease; SVD = single-vessel disease.

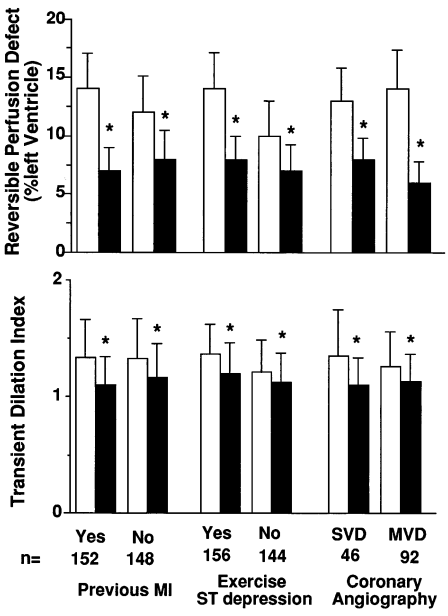


Table 3. Multivariate Predictors of Painful Reversible Perfusion Defect

Variable	Chi Square	p Value
History of effort angina	58.0	< 0.0001
Exercise ST segment depression	20.3	< 0.0001
% max age-predicted HR achieved	16.6	< 0.0001
Reversible defect extent	9.6	< 0.01
Body mass index	6.1	< 0.05
No previous MI	5.0	< 0.05

MI = myocardial infarction; other abbreviations as in Table 2.

Discussion

The subjective recognition of a cardiac ischemic stimulus is highly variable, and the proposed underlying mechanisms are still speculative. In particular, it is unclear whether a threshold of ischemic magnitude plays some role. Failure to experience angina during exercise-induced silent ischemia could be caused by inadequacy of the stimulus, due to a lesser amount of transient ischemic myocardium (1,2,9,10,21). Several other variables have been related to the absence of chest pain during ischemia, including the location and duration of the ischemic episode as well as an altered pain perception and complaint (6–8,22).

In this study we tested the hypothesis that chest pain during exercise is associated with a greater ischemic burden (as determined by quantitative tomographic criteria) than that of silent episodes. Results from our study indicate that 1) silent reversible perfusion defects occur frequently; 2) the presence of chest pain during exercise is associated with a greater ischemic burden. Furthermore, our data support the conclusion that the more evidence of ischemia patients manifest during exercise (as reflected by objective and subjective measures), the greater is their exercise-induced hypoperfusion. Patients with silent ischemia exercised for a longer time and achieved higher peak heart rate values and peak rate-pressure products on exercise testing. Thus, the absence of angina cannot be ascribed to a suboptimal stress, that is, a level of stress inadequate to bring out the symptom.

In our study, we found no differences between patients with painful and silent ischemia in the frequency of hypertension, diabetes or hypercholesterolemia, although we cannot exclude that selection bias could have influenced the distribution of conventional risk factors in this cohort of patients. Patients with symptomatic reversible hypoperfusion more frequently had a history of effort angina and, similar to a previous report (12), patients with healed myocardial infarction (whose perinecrotic or remote "anginal warning system," or both, may

Table 4. Thallium-201 Myocardial Perfusion Scintigraphic Studies Comparing the Amount of Ischemic Myocardium in Patients With or Without Chest Pain During Exercise Testing

First Author	Year	Pts (no.)	Method	Selection Criteria	Reversible Defects (% of Pts)
Amount of Ischemia Equal in Patients With or Without Chest Pain					
Hecht (11)	1989	112	SPECT	CAD; reversible defects	100%
Gasperetti (12)	1989	103	Planar	Reversible defects	100%
Heller (13)	1990	234	Planar	Reversible defects	100%
Mahamarian (14)	1990	356	SPECT	Unselected	54%*
Bandu (19)	1994	294	SPECT	Unselected	94%
Amount of Ischemia Greater in Patients With Than Without Chest Pain					
Kurata (15)	1990	471	SPECT	Unselected	37%
Galli (16)	1990	200	Planar	Old MI; reversible defects	100%
Travin (17)	1991	268	Planar	Reversible defects	100%
Hendler (18)	1992	152	SPECT	Ex ECG+	83%
Klein (9)	1994	117	SPECT	Ex ECG+	80%

*In patients with coronary artery disease (CAD). Ex ECG+ = positive exercise electrocardiogram; MI = myocardial infarction; Pts = patients; SPECT = single-photon emission computed tomography.

have been changed as a consequence of the scar) were more likely to experience silent ischemia. The use of antianginal medications, including nitrates at the time of the rest scan, was significantly more common in patients with painful ischemia (Table 1). We (23) previously reported that an improved sestamibi uptake in areas showing rest perfusion defects can occur when the tracer injection is preceded by nitroglycerin administration. Thus, we cannot exclude some underestimation of the extent of reversible hypoperfusion in patients with silent ischemia as a result of overestimating the "fixed" tracer uptake defect.

Comparison with previous studies. There is persisting uncertainty as to whether the amount of myocardium involved during an ischemic episode is similar in patients with and without pain. Conflicting data concerning differences in the degree of transient ventricular impairment (24–27) and in the angiographic extent of coronary artery disease between patients with and without exercise angina (11,14,28,29) have been reported. Discordant results have also been reported in 10 previous studies that used myocardial perfusion scintigraphy to compare the amount of ischemic myocardium in patients with and without chest pain during exercise testing (Table 4). Different imaging techniques (either planar or tomographic) and methods of analysis (either qualitative or semiquantitative) were used in these studies evaluating patients with a variety of coronary syndromes.

To our knowledge, this is the largest study comparing the degree of hypoperfusion and the presence of symptoms during exercise stress testing in a consecutive cohort of highly selected patients with ischemic heart disease. In contrast to other large studies that enrolled subjects unselectively (14,15,19) or used the presence of scintigraphic abnormalities as inclusion criteria independently of a pretest analysis of coronary artery disease probability (13,17), we focused on patients with unequivocal evidence of reversible hypoperfusion during exercise and a well established history of coronary artery disease (angiographic evidence in nearly 50% of the cohort, a history of previous myocardial infarction in an additional 20% and a high pretest probability combined with an abnormal scintigraphic scan in the remaining 33%). We used the ^{99m}Tc-labeled tracer sestamibi, whose physical characteristics are more suitable for tomographic imaging than are those of thallium-201, particularly in overweight patients. Moreover, we used a quantitative technique to assess the extent of myocardial hypoperfusion.

The occurrence of transient dilation of the left ventricle on post-stress thallium-201 (30) as well as sestamibi (31) images has been reported to be a clinically useful marker of severe and extensive coronary artery disease. Our study patients with painful ischemia also showed a greater endocardial TDI. Our sestamibi images were acquired on average 60 min after tracer injection, so it is unlikely, although not impossible, that this finding is related to a persistent myocardial stunning affecting wall motion and, through the partial volume effect, wall thickness, thus simulating a transient cavity dilation. Although the limitations of assessing ventricular volume changes solely on the basis of a midventricular short-axis view should not be disregarded, a likely cause for a greater endocardial (but not epicardial) TDI in our study is the presence of some subendocardial hypoperfusion, more pronounced in the group with painful than with silent ischemia, thus supporting the impression of a greater ischemic burden in patients with chest pain.

Pain perception and complaint. The results of this study indicate that exertional angina is related to the extent of provoked ischemia. However, the finding of severe reversible hypoperfusion was not uncommon in patients with silent exertional ischemia. One may also wonder if in our asymptomatic patients the amount of exercise-induced ischemia was not largely related to the longer exercise duration and higher peak rate-pressure product achieved. Severe exertional ischemia was silent in nearly 50% of the cases. It is unclear how much

the nature of the ischemic stimulus itself or the cognitive mechanisms for perceiving and reporting the symptom determine whether an event is painful (5,6,10,22). More attention has been recently focused on regional brain activation in response to noxious stimuli (7) as well as the interactions between behavioral patterns and the cognitive processes influencing perception of ischemic symptoms (8,22). Conflicting results have been reported (22,32,33) concerning the psychologic correlates of sensitivity to painful symptoms and symptom-reporting behavior in the patient with silent or symptomatic ischemia. There is now some evidence (7) that the absence of pain during myocardial ischemia may be related to an abnormal central nervous system handling of afferent nociceptive messages. Rosen et al. (7) compared changes in regional cerebral blood flow during symptomatic and silent myocardial ischemia. Despite a comparable degree of thalamic activation shown in both angina and silent ischemia, they found a lesser extent of cortical activation in patients with painless ischemia, suggesting some gating of afferent stimuli at the thalamic level. The complex interaction between location and size of the myocardial ischemic burden, behavioral patterns and the cognitive processes handling the ischemia-related signals was recently discussed by Pepine (8).

Study limitations. In this study, we adopted the scintigraphic finding of a reversible sestamibi uptake defect as the reference standard for exercise-induced ischemia. This assumption is widely accepted in clinical practice. Compared with angiographic results, a reversible scintigraphic perfusion defect better predicts the hemodynamic significance of a stenosis, in terms of both transstenotic gradient (34) and reduced coronary reserve (35). In experimental models (36), the finding of a reversible scintigraphic uptake defect suggests an underlying ischemic process. On the contrary, when considering the reliability of a reversible perfusion tracer uptake defect as a marker of transient ischemia, the risk of underestimating the true extent of hypoperfusion in patients with severe and extensive coronary disease should be emphasized (35). Furthermore, we did not assess whether the different amount of jeopardized myocardium observed in asymptomatic or painful inducible ischemia could have different prognostic implications.

Despite these limitations, the present study adds important information on the relation between the degree of the ischemic injury and symptoms during exercise-induced myocardial ischemia. Chest pain during exercise was associated with objective measures clearly indicating a greater ischemic burden.

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